

**REMARKS**

Claims 1-4, 6-17 and 19-34 are pending. By virtue of this response, no claims are being canceled, added, or amended. Claims 16, 17, and 19-31 are withdrawn. Therefore, claims 1-4, 6-15, and 32-34 are presently under examination.

**I. Claim Rejections Under 35 USC §103 – Bardotti in view of Hennion**

Claims 1-9 and 32-34 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Bardotti et al. (Vaccine 18: 1982-1993, 2000) in view of Hennion, MC. (Journal of Chromatography A, vol.856, pp. 3-54, 1999).

Applicants respectfully traverse the rejection and its supporting remarks.

Before addressing the Examiner's substantive comments regarding the rejection, Applicants wish to clear up an apparent misunderstanding. The Examiner stated that "[i]n response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on a combination of references" (6/21/11 Office Action, page 6). Applicants respectfully note that, in the Office Action response filed March 22, 2011, Applicants were not attempting to attack the references individually. Rather, the Applicants were merely pointing out that neither Bardotti nor Hennion in any way refers to the other, so there is no express teaching to combine the references to arrive at the claimed invention (*i.e.*, Hennion does not teach or suggest that the techniques are useful for separating unconjugated saccharides from conjugated saccharides and Bardotti does not teach or suggest that solid phase extraction may be a useful alternative to the methods used by Bardotti).

**A. Application Disclosure**

As discussed on page 2, lines 7-16 and elsewhere in the specification, the inventors have found a method for quickly and reproducibly separating conjugated capsular saccharides from unconjugated capsular saccharides, through the use of solid phase extraction (SPE). Separation of conjugated capsular saccharides from unconjugated saccharides is important, for example, for the analysis and quality control of vaccines which contain conjugated capsular saccharides. Prior to the present disclosure, various methods for separating unconjugated capsular saccharides from

conjugated capsular saccharides were available (e.g. ultrafiltration, hydrophobic chromatography, and selective precipitation). However, these techniques suffered from various drawbacks (specification, page 1, lines 34-35 through page 2, lines 1-2). By contrast, the SPE-based method of the present disclosure for separating conjugated capsular saccharides from unconjugated capsular saccharides has multiple advantages over previously known techniques (page 2, lines 9-11).

*B. The Examiner Fails to Provide an Adequate Reason to Combine Bardotti and Hennion to Arrive at the Claimed Invention*

In the Office Action dated June 21, 2011, the Examiner states that the Applicant's arguments regarding the non-obviousness of Bardotti in view of Hennion presented in the Office Action response filed March 22, 2011 were "fully considered but...not persuasive." (Office Action, page 4). The Examiner then provides various reasons that it would allegedly be obvious for one of skill in the art combine Bardotti and Hennion to arrive at the claimed invention. Applicants respectfully assert that none of these reasons provides an adequate basis for one of skill in the art to combine the references to arrive at the invention of the present claims.

As an initial matter, Applicants respectfully assert that the Examiner has improperly assessed the obviousness of the claimed invention by focusing the obviousness analysis on the content of Hennion, rather than on the problems faced by the inventors. In particular, the Examiner's obviousness analysis fails to provide any reason that one of skill in the art interested in methods for the separation of conjugated capsular saccharides from unconjugated capsular saccharides would be motivated to select SPE over many other possible techniques. As described in the present disclosure and as would have been known by one of skill in the art, there are many different methods available in the art that could be tested as an alternative means of separating conjugated capsular saccharides from unconjugated capsular saccharides. One of skill in the art interested in improving the separation of saccharides after reading Bardotti would not immediately and exclusively look to SPE (or any other particular technique). Rather, one of skill in the art would consider multiple possible methods for the separation of conjugated capsular saccharides from unconjugated capsular saccharides, in order to attempt to develop an improved method for the separation of saccharides. Furthermore, one of skill would not arbitrarily change an established

method for the separation of saccharides, without a clear indication that a new method would be beneficial. Instead of taking these factors into account, the Examiner has simply looked in Hennion for possible benefits of SPE relating to methods for the separation of conjugated capsular saccharides from unconjugated capsular saccharides. Applicants respectfully assert that this analysis improperly omits the important step of providing a reason why one of skill would have been motivated to select SPE over many other possible techniques for the separation of saccharides (including techniques already being used by Bardotti and others). Applicants further respectfully assert that it would not have been obvious for one of skill in the art to apply the teachings of Hennion to the method of Bardotti, given the wide range of possible techniques available to one of skill in the art for the separation of saccharides such as hydrophobic interaction chromatography, size exclusion chromatography, ammonium sulfate precipitation, etc.

Turning to the reasons raised by the Examiner, the Examiner states that in addition to teaching that SPE is a popular technique, Hennion teaches other advantages of SPE that would have provided a reason for one of skill in the art to use SPE in the method of Bardotti to obtain the claimed invention. The Examiner cites to four “other advantages” of SPE disclosed in Hennion besides it being a popular technique, which are discussed in turn below. Applicants respectfully assert that none of these features of SPE provide an adequate reason for one of skill in the art to use SPE in the method of Bardotti.

#### 1. SPE can be automated

The fact that SPE can be automated does not provide an adequate reason for one of skill in the art to apply SPE to a method for the separation of conjugated capsular saccharides from unconjugated capsular saccharides.

First, there is no indication in Bardotti that lack of automation was a problem for the separation of conjugated capsular saccharides from unconjugated capsular saccharides. Since the method of Bardotti is commonly used for quality control purposes of vaccines, frequently, only a small number of samples are analyzed at a time. Accordingly, there is no indication that automation would be advantageous to the method of Bardotti, or that one of skill would have a compelling reason to develop a means for automation of separation of saccharides.

Second, even if there would be a benefit to automation of methods for the separation of conjugated capsular saccharides from unconjugated capsular saccharides, other techniques available for this separation can also be automated. For example, hydrophobic interaction chromatography, which was mentioned by the inventors in the specification as a known method for the separation of conjugated capsular saccharides from unconjugated capsular saccharides (specification, page 1, line 35) is similar to SPE and therefore could be automated to the same degree. Thus, the fact that SPE can be automated also does not provide any reason for one of skill in the art to use SPE in the method of Bardotti, as other techniques (including techniques already in use in the art) could also be automated.

2. SPE provides a large choice of sorbents for trapping analytes over a wide range of polarities

The fact that SPE provides a large choice of sorbents for trapping analytes over a wide range of polarities also is not an adequate reason for one of skill to apply SPE to the method of Bardotti. Conjugated and unconjugated saccharides are both water-soluble. Thus, separation would not require special solvents or trapping of analytes over a wide range of polarities. Thus, the “large choice of sorbents” of SPE would not be advantageous to one of skill in the art for separation of saccharides. Moreover, techniques already existed for trapping analytes of the relevant polarities, as methods for the separation of conjugated capsular saccharides from unconjugated capsular saccharides were already known at the time of the present invention. Accordingly, the availability of a large choice of SPE sorbents for trapping analytes over a wide range of polarities presents no advantages over the methods available in the art for the separation of saccharides.

3. Hennion provides details to determine the main parameters of any sequence (type and amount of sorbent, sample volume which can be applied without loss of recovery, ...)

The teachings of Hennion regarding the main parameters of SPE also do not provide an adequate reason for one of skill to apply SPE to the separation of conjugated capsular saccharides from unconjugated capsular saccharides. This content of Hennion is essentially technical information regarding details of various SPE parameters. Technical information regarding SPE does not provide any reason for one of skill in the art who is not using SPE to begin using SPE.

Rather, such information is only useful for a person of skill who has already decided to use SPE or is considering SPE, and who is seeking to learn more about details of SPE. Put another way, this technical information is irrelevant to whether SPE would provide for superior separation of conjugates from unconjugated saccharides. Accordingly, this content of Hennion is not an “advantage” that would provide a reason for one of skill in the art to apply SPE to the method of Bardotti.

4. Extracts free from matrix interferences may be prepared “in a few steps - one step when possible”

The fact that materials may be separated by SPE in a few steps, and in some cases, one step, also does not provide an adequate reason for one of skill to apply SPE to the method of Bardotti. One step separation of conjugated capsular saccharides from unconjugated capsular saccharides already existed in the method of Bardotti, in which the saccharides were separated by ultracentrifugation. Accordingly, a person of skill interested in one step separation of saccharides would have no reason to switch to SPE, since the method of Bardotti already provided one step separation. Moreover, other known techniques available in the art also allowed for the separation of conjugated capsular saccharides from unconjugated capsular saccharides in a single step (e.g. selective precipitation; discussed below). Thus, this teaching of Hennion is also not an “advantage” that would provide a reason for one of skill to apply SPE to the separation of conjugated capsular saccharides from unconjugated capsular saccharides. At best, SPE is no worse than existing one step methods, and could even be worse since Hennion acknowledges that some materials require more than one step to separate them.

In summary, none of the “advantages” of SPE presented in Hennion provide an adequate reason for one of skill to modify Bardotti in view of Hennion. The cited “advantages” of SPE presented in Hennion were all either already available in the art for the separation of saccharides (e.g. one-step separation of saccharides; methods may be automated), or they were not relevant to the problem of methods for the separation of saccharides (e.g. SPE provides a large choice of sorbents; Hennion provides technical details regarding SPE methods) at the time of the present invention. Furthermore, most of the cited “advantages” of SPE cited in Hennion would be available

with other techniques besides SPE (e.g. one-step separation of saccharides; fully automatable methods; a range of chromatographic sorbets; publications that provide technical information), and the Examiner has provided no reason that one of skill would have applied SPE instead of another technique to the method of Bardotti. Accordingly, Hennion does not provide any information that would have provided a reason for one of skill in the art to use a SPE device in the method of Bardotti to obtain the instant invention.

Accordingly, Applicants respectfully assert that for at least these reasons, it would not have been obvious for one having skill in the art to combine Bardotti and Hennion to arrive at the claimed invention.

Applicants therefore respectfully request that the Examiner withdraw the rejection of claims 1-9 and 32-34.

## **II. Claim Rejections Under 35 USC §103 – Lei in view of Hennion**

Claims 1-15 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Lei et al. (Dev. Biol (Basel) vol. 103, pp. 259-264, 2000) in view of Hennion, MC. ( Journal of Chromatography A, vol.856, pp. 3-54, 1999).

Applicants respectfully traverse the rejection and its supporting remarks.

### **The Examiner Fails to Provide an Adequate Reason to Combine Lei and Hennion to Arrive at the Claimed Invention**

In the Office Action dated June 21, 2011, the Examiner states that the Applicant's arguments regarding the non-obviousness of Lei in view of Hennion presented in the Office Action response filed March 22, 2011 were "fully considered but...not persuasive." (Office Action, page 8). The Examiner then provides various reasons that it would allegedly be obvious for one of skill in the art combine Lei and Hennion to arrive at the claimed invention. Applicants respectfully assert that none of these reasons provides an adequate basis for one of skill in the art to combine these references to arrive at the invention of claims 1-15, for the same reasons discussed above regarding Bardotti.

As with the rejection over Bardotti in view of Hennion, the Examiner has stated that “[i]n response to applicant’s arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on a combination of references” (6/21/11 Office Action, page 9). Applicants respectfully note that in the Office Action response filed March 22, 2011 Applicants were not attempting to attack the references individually. Rather, the Applicants were merely pointing out that neither Lei nor Hennion in any way refers to the other, so there is no express teaching to combine the references to arrive at the claimed invention.

The Examiner has asserted that it would have been prima facie obvious to one of ordinary skill in the art at the time of the invention to use a SPE device in the method of Lei to obtain the claimed invention. As discussed above, Applicants respectfully assert that the Examiner has failed provide any reason that one of skill in the art interested in the separation of conjugated capsular saccharides from unconjugated capsular saccharides would be motivated to select SPE over many other possible techniques. Applicants respectfully assert that the Examiner has improperly simply looked in Hennion for possible benefits of SPE relating to methods for the separation of conjugated capsular saccharides from unconjugated capsular saccharides, and has not provided a reason why one of skill in the art would be motivated to combine SPE (rather than other techniques) with the method of Lei.

Turning to the specific reasons to combine raised by the Examiner, the Examiner asserts that in addition to teaching that SPE is a popular technique, Hennion teaches other advantages of SPE that would have provided a reason for one of skill in the art to use SPE in the method of Lei to obtain the claimed invention. The Examiner cites to the same four “other advantages” of SPE disclosed in Hennion, which are discussed at length above regarding Bardotti. Applicants respectfully assert that for the same reasons discussed above regarding Bardotti, none of the “advantages” of SPE presented in Hennion provide an adequate reason for one of skill to modify Lei in view of Hennion. For example, Applicants note that Lei also teaches a one-step method for the separation of conjugated capsular saccharides from unconjugated capsular saccharides (by selective precipitation). Accordingly, Hennion does not provide any information that would have given one of skill reason to use a SPE device in the method of Lei to obtain the instant invention.

Accordingly, Applicants respectfully assert that for at least these reasons, it would not have been obvious for one having skill in the art to combine Lei and Hennion to arrive at the claimed invention.

Applicants therefore respectfully request that the Examiner withdraw the rejection of claims 1-15.



**CONCLUSION**

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing **Docket No. 223002118900**. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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